CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74929

BIOEQUIVALENCE REVIEW(S)

Etodolac
300 mg Capsules
ANDA #**74-929**
Reviewer: Z.Z. Wahba
File #74929a.897

Aesgen, Inc.
Wilmington, NC
Submission Date:
August 19, 1997

AMENDMENT TO A REVIEWED IN VIVO BIOEQUIVALENCE STUDY UNDER FASTING AND NON-FASTING CONDITIONS

BACKGROUND

1. The firm has previously submitted in vivo bioequivalence studies under fasting and non-fasting conditions comparing its 300 mg Etodolac Capsules to the reference drug product Lodine® 300 mg Capsules (Wyeth-Ayerst).

2. The submission was reviewed and was found incomplete by the Division of Bioequivalence (review dated March 24,1997, ANDA #74-929) due to deficiency comments.

3. In this submission, the firm has responded to the deficiency comments and included additional information in the current submission.

COMMENT #1

Dissolution testing conducted by Aesgen Inc. on its etodolac 300 mg Capsules does not meet the agency specifications. The firm has determined dissolution of the test products in 900 mL of pH 7.5 phosphate buffer with pancreatin enzyme, at 37°C using USP 23 apparatus II (Paddles), 50 rpm with limits of not less than (Q), dissolved in 45 minutes, instead of the agency specifications.

There is no USP dissolution testing procedure specified for etodolac capsules. Therefore, the sponsor should conduct dissolution testing following the Agency specifications.

The firm should conduct the dissolution testing applying a spectroscopy assay method and using USP 23 apparatus I (Basket) at 100 rpm in 1000 mL of pH 7.5 phosphate buffer at 37°C. The sampling time should be 5, 10, 20 and 30 minutes. The dissolution testing should meet the following specifications:

Not less than (Q) of the labeled amount of the drug product in the capsule is dissolved in 30 minutes.

The dissolution should be conducted for both the test and reference products, performed simultaneously. The lot number of the dissolution testing should be identical to the one used in the in vivo bioeqivalence study.

RESPONSE TO COMMENT #1

Dissolution Testing:

Method: USP 23 apparatus I (Basket) at 100 rpm
Medium: 1000 mL of pH 7.5 phosphate buffer
Number of Units: 12 Capsules
Test products: Aesgen's Etodolac 300 mg Capsules, lot #MNC0011
Reference products: Wyeth-Ayerst's Lodine® 300 mg Capsules, lot #3940275
Specifications: NLT in 30 minutes.

Dissolution testing results are shown in the following Table.

Table. In Vitro Dissolution Testing

Drug (Generic Name): Etodolac Capsules
Dose Strength: 300 mg
ANDA No.: 74-929
Firm: Aesgen, Inc.
Submission Date: August 19,1997
File Name: 74929a.897

I. Conditions for Dissolution Testing:

USP XXII Basket:X Paddle: RPM: 100
No. Units Tested: 12 Capsules
Medium: 1000 mL of phosphate buffer pH 7.5
Specifications: NLT in 30 minutes
Reference Drug: Wyeth-Ayerst's Lodine®

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # MNC0011 Strength(mg) 300			Reference Product Lot # 3940275 Strength(mg) 300		
	Mean %	Range	%CV	Mean %	Range	%CV
5	19.5		40.5	38.9		29.6

10	44.9		34.8	84.1		10.4
20	82.0		22.0	99.1		2.1
30	98.3		2.7	100.4		3.1

The dissolution data for the test product is acceptable.

The firm's response to comment #1 is acceptable.

COMMENT #2

The dissolution data that are provided on page #1525, volume C1.5 are for lot #MNC001V whereas the bioequivalence study was conducted on lot #MNC0011. The firm should check its documents for the correct lot number.

RESPONSE TO COMMENT #2

The firm indicated that the control numbering system used at the manufacturing site serves to identify the drug product through all stages of manufacturing, packaging, etc. Lot #MNC001V is the number assigned to bulk drug before packaging. Upon packing into bottles of 100, the letter "V" is substituted by number "1" so the packaged product is assigned lot #MNC0011.

The firm's response to comment #2 is acceptable.

REVIEWER'S COMMENTS:

1. Under fasting conditions: The firm's in vivo bioequivalence study under fasting conditions demonstrated that the test product, Aesgen's Etodolac Capsule 300 mg is bioequivalent to the reference product, Wyeth-Ayerst's Lodine® Capsule 300 mg. The 90% confidence intervals for the log-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were all within the acceptable range of 80-125%.

2. Under non-fasting conditions: The firm's in vivo bioequivalence study under non-fasting conditions demonstrated that the test product, Aesgen's Etodolac Capsule 300 mg is bioequivalent to the reference product, Wyeth-Ayerst's Lodine® Capsule 300 mg. The ratios of the test mean to the reference mean for the AUC_{0-t}, $AUC_{0-\infty}$, C_{max} were within the acceptable range of 0.8-1.25.

3. The firm has provided acceptable comparative dissolution data for its drug product, Aesgen's Etodolac Capsule 300 mg. The firm conducted the dissolution test using FDA methodology.

RECOMMENDATION

1. The two bioequivalence studies conducted by Aesgen, Inc., under fasting and non-fasting conditions on its drug product, Etodolac Capsules, 300 mg (lot #MNC0011), comparing it to Wyeth-Ayerst's Lodine® Capsules, 300 mg have been found acceptable by the Division of Bioequivalence. The studies demonstrate that Aesgen's Etodolac Capsule 300 mg is bioequivalent to the reference product, Wyeth-Ayerst's Lodine® Capsule 300 mg.

2. The dissolution testing conducted by the firm on its Etodolac Capsules, 300 mg (lot #MNC0011) has been found acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 1000 mL of phosphate buffer pH 7.5 at 37°C using USP 23 apparatus I (Basket) at 100 rpm. The test product should meet the following specifications:

   Not less than of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

The firm should be informed of the above recommendation.

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE

12/16/97

Concur: Date: 12/23/97

Dale Conner, Pharm.D.
Director
Division of Bioequivalence

cc: ANDA #74-929, (original, duplicate), HFD-658 (Mhatre, Wahba),

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 74-929 APPLICANT: Aesgen, Inc.

DRUG PRODUCT: Etodolac Capsules, 300 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

MAR 24 1997

Etodolac
300 mg Capsules
ANDA #**74-929**
Reviewer: Z.Z. Wahba
File #74929sd.796

Aesgen, Inc.
Wilmington, NC
Submission Date:
July 23, 1996

REVIEW OF TWO IN-VIVO BIOEQUIVALENCE STUDY AND IN VITRO DISSOLUTION TESTING DATA

I. OBJECTIVE:

Review the following:

1. Aesgen's in vivo bioequivalence study under fasting and non-fasting conditions comparing its 300 mg Etodolac Capsules to the reference drug product Lodine® 300mg Capsules (Wyeth-Ayerst).

2. Dissolution data for the test and reference drug products.

II. INTRODUCTION:

Etodolac is a nonsteroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and antipyretic activities. The drug is a racemic mixture of R-and S-etodolac, the S-form being biologically active. Both enantiomers are stable and there is no R-to-S conversion in-vivo. Etodolac is more than 99% bound to plasma proteins. The free fraction is less than 1% and is independent of etodolac total concentration. When administered orally, etodolac exhibits characteristics which are well described by a two-compartment model with first-order absorption. The systemic availability of etodolac is at least 80% and the drug does not undergo significant first-pass metabolism. Mean (±1 SD) peak plasma concentrations range from approximately 14 ±4 to 37 ±9 ug/ml after 200 to 600 mg single doses and are reached in 80 ±30 minutes. Terminal half-life is 7 ±4.0 hours. Inter subject variability of etodolac plasma levels, achieved after recommended doses, is substantial.

The extent of absorption of etodolac is not affected when etodolac is administered after a meal or with an antacid. Food intake, however, reduces the peak concentration by approximately one half and increases the time to peak concentration by 1.4 to 3.8 hours.

The recommended dose of etodolac for acute pain is 200 to 400 mg every 6 to 8 hours, as needed, not to exceed a total daily dose of 1200 mg. Lodine® (Wyeth-Ayerst) is the innovator product and marketed strengths include 200 and 300 mg capsules and 400 mg tablets.

III. BIOEQUIVALENCE STUDY UNDER FASTING CONDITION
Clinical Study #P95-341

A. Sponsor:

Aesgen, Inc.
5051 New Center Drive, Suite 103
Wilmington, NC 28403

Clinical Study Dates:
Period I: March 10-11, 1996
Period II: March 17-18, 1996

B. Study design:

Single dose, randomized, two-way crossover study under fasting conditions.

C. Subjects:

Twenty-six (26) healthy male subjects were enrolled in the study but 24 subjects completed the study (subjects #1-17 and 20-26). The subjects were in the range of 18 to 45 years of age, and their body weights were within ± 10% of the ideal weight as defined by the Metropolitan Life Insurance Chart.

Subject Selection Criteria:

Only medically and physically healthy subjects with clinically normal ranges of laboratory tests (blood chemistry, hematology, urinalysis) were enrolled in the study.

Subject Exclusion Criteria:

- A history of chronic alcohol or drug addiction.
- A history of cardiovascular, gastrointestinal, renal, hepatic, pulmonary, neurological or hematological disease.
- Subjects with any clinically significant illness during the 4 weeks prior to period I dosing.
- A history of allergic responses to the class of drug being tested.
- Use of tobacco in any form.
- Blood donation within the past 30 days prior to the study.
- Use of any investigational drug within 30 days preceding entry into the study.

Subject Restrictions:

- No subject took any medications, including OTC products for at least one week prior to the beginning of the study and until completion of the study.
- No alcoholic, xanthine and caffeine containing foods and beverages were allowed, beginning with 48 hours prior to dosing and until completion of the study.

D. Food and Fluid Intake:

Subjects fasted overnight for at least 10 hours before dosing and 4 hours after dosing. Water was allowed from 1 hour prior to dose administration until 2 hours after dosing. The subjects received their medication with 240 mL of water according to randomized dosing schedule. Standard meals were provided at appropriate times thereafter.

E. Treatment:

Test product: 1 X 300 mg Etodolac Capsule (Aesgen), Lot #MNC0011, Batch size assay potency 99.0%, content uniformity 99.9% (CV=0.9%), manufacturing date: 01/11/96.

Reference product: 1 X 300 mg Lodine® Capsule (Wyeth-Ayerst), Lot #3940275, assay potency 98.7%, content uniformity (not given), expiration date: 02/97.

Washout period: 7 days.
A single 300 mg dose was given in each period of the study.

F. **Blood Sampling**:

Blood samples were collected in vacutainers with EDTA, before dosing (0 hour) and at 0.25, 0.50, 0.75, 1.0, 1.33, 1.67, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12, 16, 24, 30 and 36 hours post-dosing. The plasma samples were separated, collected and stored frozen at -20°C until analysis.

G. **Assay Methodology**:

H. In Vivo BE Study and Statistical Analysis (Under Fasting Conditions)

Twenty-six (26) healthy male subjects were enrolled in the study but 24 subjects completed the study (subjects #1-17 and 20-26). Subjects #18 and #19 failed to report for Period II check-in. Failure to complete the study was not related to study product. The pharmacokinetic parameters of etodolac were analyzed using SAS (GLM procedure) for analysis of variance. The pharmacokinetic parameters for the plasma etodolac concentrations, as well as the following parameters, AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, K_{el}, $t_{1/2}$ are summarized in the tables below:

Table 4

Mean Plasma Concentrations (μg/mL) of Etodolac in 24 Subjects Following a Single Oral Dose of 300 mg Etodolac Under Fasting Conditions

(Test-Lot #MNC0011, Reference-Lot #3940275)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.25	1.21	1.69	0.77	0.87	1.57
0.5	11.10	6.79	6.88	5.85	1.61
0.75	15.32	8.97	11.46	8.53	1.34
1	15.06	8.14	13.47	8.63	1.12
1.33	13.71	5.51	14.10	7.69	0.97
1.67	13.92	5.54	14.27	5.02	0.98
2	13.15	4.63	14.36	5.22	0.92
2.5	12.78	3.86	13.05	3.95	0.98
3	11.71	3.70	12.02	3.42	0.97
4	9.14	3.08	9.00	2.75	1.02
6	4.42	1.25	4.15	1.15	1.07
8	3.24	0.96	3.03	0.88	1.07
12	2.03	0.74	1.90	0.70	1.07
16	1.26	0.50	1.18	0.53	1.07
24	0.67	0.36	0.59	0.35	1.14
30	0.32	0.34	0.22	0.23	1.42
36	0.16	0.24	0.09	0.22	1.75

MEAN1= Test MEAN2=Reference RMEAN12=T/R ratio

Table 5

Mean Pharmacokinetic Parameters (Arithmetic) in 24 Subjects Following a Single Oral Dose of 300 mg Etodolac Under Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	101.13	27.49	93.97	24.94	1.08
AUCT	95.39	25.08	90.01	23.77	1.06
CMAX	21.57	5.22	20.88	5.01	1.03
KE	0.10	0.03	0.11	0.02	0.94
*LAUCI	97.63	0.27	90.82	0.27	1.07
*LAUCT	92.29	0.26	86.97	0.27	1.06
*LCMAX	20.91	0.26	20.30	0.25	1.03
THALF	7.40	2.00	6.88	1.57	1.08
TMAX	1.47	0.81	1.80	0.90	0.82

MEAN1=Test MEAN2=Reference RMEAN12=T/R ratio

* The values represent the geometric means (antilog of the means of the logs).

Table 6
LSMeans And The 90% Confidence Intervals
(Under Fasting Conditions)

	LSM1	LSM2	LOWCI12	UPPCI12
PARAMETER				
*LAUCI	96.63	90.82	98.76	114.61
*LAUCT	92.29	86.97	98.65	114.16
*LCMAX	20.91	20.30	92.60	114.59

UNIT: AUC=μG HR/ML CMAX=μG/ML
Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R
* The values represent the LSMEANS (antilog of the means of the logs).

Table 7
Test/Reference Products Ratios for Pharmacokinetic Parameters for Individual Subjects
(Under Fasting Conditions)

OBS	SUB	SEQ	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
1	1	2						
2	2	1						
3	3	2						
4	4	1						
5	5	2						
6	6	2						
7	7	2						
8	8	2						
9	9	1						
10	10	1						
11	11	2						
12	12	2						
13	13	1						
14	14	2						
15	15	2						
16	16	1						
17	17	1						
18	20	1						
19	21	1						
20	22	2						
21	23	1						
22	24	1						
23	25	1						
24	26	2						

1=Test product 2=Reference product

Table 8
Statistics on Individual Test/Reference Ratios for Pharmacokinetic Parameters (Under Fasting Conditions)

Variable	N	Mean	Std Dev	Minimum	Maximum
RAUCT12	24	1.08	0.20	0.55	1.56
RAUCI12	22	1.08	0.21	0.56	1.56
RCMAX12	24	1.08	0.31	0.50	1.57
RTMAX12	24	0.94	0.58	0.17	3.00
RKE12	22	0.97	0.22	0.57	1.35
RTHALF12	22	1.09	0.26	0.74	1.77

1. The mean plasma etodolac levels reached a maximum level of concentration between 0.75-2.0 hours (Table #4 and Figures #1 and 2).

2. The 90% confidence intervals for the LSMeans log-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} were within the acceptable range of 80-125% (Table #6). The T/R mean ratios for the log-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} were 1.06, 1.07 and 1.03, respectively (Table #5).

   There were no significant sequence, period or treatment effects of the test and reference drug treatments for the log-transformed pharmacokinetic parameters AUC_{0-t} and C_{max}.

3. Test/reference ratios for individual subjects
   The test/reference ratios shown in Table #7 were summarized in Table #8. The mean ratios for AUCT, AUCI and CMAX were all 1.08 with 18.5% CV, 19.4% CV and 28.7% CV, respectively. This indicates that the test product's AUCT, AUCI and CMAX for the individuals are 8% higher for each parameter than the reference product's AUCT, AUCI and CMAX. The percentage of change of the test mean to the reference mean for the AUC_{0-t}, $AUC_{0-\infty}$, C_{max} are acceptable.

   Note: RAUCI12, RKE12 and RTHALF12 values for Subjects #7 and #8 were not avaliable because their KE value cannot be calculated. The terminal elimination rate (KE) cannot be obtained from the slope of the log-linear least-square regression line of the the terminal points of the concentration versus time profile.

I. **Adverse Events**:
   The adverse reactions are reported on page #191, Vol. C1.2, section `Clinical Summary'.

Parameter	Test/# subj.	Ref./# subj.
Coughing	1	2

Headache	1	2
Malaise (Body Aches)	2	--
Pharynigits (Sore Throat)	1	1
Purpura (Bruise Left Arm)	--	1
Respiratory Disorder (Head Congestion)	--	1
Rhinitis (Runny Nose)	--	3
Rigors (Chills)	--	1

Non of the adverse events were considered serious or related in terminating any subject from study participation.

Protocol Deviation: (On page #190, vol. C1.2)
Subject #17 had a sore throat and cough, and medication was used. In the opinion of the clinical investigator, the problem and medication usage was not related to study participation and should not affect the integrity of the study.

IV. BIOEQUIVALENCE STUDY UNDER NON-FASTING CONDITIONS (clinical study project #P95-345)

A. Sponsor:

Aesgen, Inc.
5051 New Center Drive, Suite 103
Wilmington, NC 28403

Clinical Study Dates:
Period I: March 02-03, 1996
Period II: March 09-10, 1996

Period III: March 16-17, 1996

B. **Study design**:

Randomized, three-way crossover, single dose study, under fasting and non-fasting conditions.

C. **Subjects**:

Eighteen (18) healthy male subjects were enrolled and completed the study (subjects #1-18). The subjects were in the range of 18 to 45 years of age, and their body weights were within ± 10% of the ideal weight as defined by the Metropolitan Life Insurance Chart.

Subject Selection, Exclusion and Restrictions Criteria:
Same as in Protocol #P95-341 (under fasting conditions).

D. **Treatment**:

Test product A: 1 X 300 mg Etodolac Capsule (Aesgen), Lot #MNC0011, Batch size assay potency 99.0%, content uniformity 99.9% (CV=0.9%), manufacturing date: 01/11/96, under fasting conditions.

Test product B: 1 X 300 mg Etodolac Capsule (Aesgen), Lot #MNC0011, Batch size assay potency 99.0%, content uniformity 99.9% (CV=0.9%), manufacturing date: 01/11/96, under non-fasting conditions.

Reference product C: 1 X 300 mg Lodine® Capsule (Wyeth-Ayerst), Lot #3940275, assay potency 98.7%, content uniformity (not given), expiration date: 02/97, under non-fasting conditions.

Washout period: 7 days.
A single 300 mg dose was given in each period of the study.

E. **Food and Fluid Intake**:

Subjects who received treatment A, fasted overnight for 10 hours before dosing and for 4 hours after drug administration. Subjects who were fed standard recommended breakfast prior to dosing (treatments B and C) only fasted for 9.5 hours. Treatments B and C differed from treatment A in that the subjects were fed a standard high fat breakfast, which was consumed in its entirety 30 minutes before drug administration. The standard breakfast meal contained the following: one buttered English muffin, one fried egg, one slice of American cheese, one slice of Canadian bacon, one serving of hashed brown potatoes, eight fluid ounces (240 ml)

of whole milk and six fluid ounces (180 ml) of orange juice. Each dose was followed by 8 fluid ounces (240 mL) of room temperature tap water according to randomized dosing schedule. Water was permitted ad lib until 1 hours before dosing and again at 2 hours after dosing. Standard meals were provided at appropriate times thereafter.

F. Blood Sampling:

Blood samples were collected in vacutainers with EDTA, before dosing (0 hour) and at 0.25, 0.50, 0.75, 1.0, 1.33, 1.67, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12, 16, 24, 30 and 36 hours post-dosing. The plasma samples were separated, collected and stored frozen at -20°C or lower until analysis.

G. Assay Methodology:

Same as in Protocol #P95-341 (under fasting conditions).

H. In Vivo BE Study and Statistical Analysis (Under Non-Fasting Conditions)

Eighteen (18) healthy male subjects were enrolled and completed the study (subjects #1-18). The pharmacokinetic parameters of etodolac were analyzed using SAS (GLM procedure) for analysis of variance. The pharmacokinetic parameters of the plasma etodolac concentrations, as well as the following parameters, AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, K_{el}, $t_{1/2}$ are summarized in the tables below:

Table 9
Mean Plasma Concentrations of Etodolac (μg/mL) in 18 Subjects Following 300 mg Oral Doses of Etodolac Under Non-Fasting Conditions
(Test-Lot #MNC0011, Reference-Lot #3940275)

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
TIME HR							
0	0.00	0.00	0.00	0.00	0.00	0.00	.
0.25	1.11	1.82	0.00	0.00	0.02	0.08	.
0.5	8.99	7.01	0.35	0.64	0.17	0.38	26.05
0.75	17.19	8.00	1.11	1.90	0.62	0.88	15.54
1	19.29	5.78	1.98	3.37	1.36	1.61	9.74
1.33	17.29	4.21	2.72	3.51	2.47	2.59	6.37
1.67	14.75	2.95	3.95	3.47	3.48	3.40	3.74
2	12.97	2.69	5.88	3.27	4.39	3.60	2.21
2.5	11.74	2.78	7.05	2.84	6.08	3.02	1.66
3	10.20	2.37	8.47	3.27	8.14	3.18	1.20
4	7.83	1.78	9.70	3.14	11.23	3.07	0.81
6	3.83	0.65	6.24	2.30	6.86	2.29	0.61
8	2.87	0.56	4.14	1.34	4.30	1.41	0.69
12	1.86	0.39	2.29	0.75	2.31	0.63	0.81
16	1.14	0.33	1.36	0.51	1.36	0.48	0.83
24	0.54	0.25	0.71	0.35	0.70	0.35	0.75
30	0.22	0.27	0.31	0.27	0.28	0.33	0.69
36	0.07	0.15	0.06	0.14	0.13	0.20	1.25

(CONTINUED)

TIME HR	RMEAN13	RMEAN23
0	.	.
0.25	60.30	3.00
0.5	53.92	2.07
0.75	27.60	1.78
1	14.17	1.45
1.33	7.00	1.10
1.67	4.24	1.14
2	2.95	1.34
2.5	1.93	1.16
3	1.25	1.04
4	0.70	0.86
6	0.56	0.91
8	0.67	0.96
12	0.80	0.99
16	0.83	1.00
24	0.77	1.01
30	0.77	1.12
36	0.56	0.45

1=Test-Fast 2=Test-NonFast 3=Ref.-NonFast
UNIT: PLASMA LEVEL=μG/ML TIME=HRS

Table 10
Mean Pharmacokinetic Parameters
in 18 Subjects Following a Single Oral Dose of
300 mg Etodolac Under Non-Fasting Conditions

PARAMETER	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
AUCI	93.66	15.99	83.95	17.00	86.66	16.21	1.12
AUCT	88.58	15.12	78.41	17.06	80.60	15.35	1.13
CMAX	22.50	5.07	10.79	2.93	11.75	2.87	2.09
KE	0.11	0.02	0.10	0.02	0.11	0.03	1.03
*LAUCI	92.38	0.17	82.65	0.17	85.42	0.17	1.12
*LAUCT	87.39	0.17	76.99	0.19	79.36	0.18	1.14
*LCMAX	21.97	0.22	10.42	0.27	11.45	0.23	2.11
THALF	6.83	1.70	7.05	1.68	6.72	1.61	0.97
TMAX	1.21	0.53	3.31	1.46	3.56	0.78	0.37

PARAMETER	RMEAN13	RMEAN23
AUCI	1.08	0.97
AUCT	1.10	0.97
CMAX	1.91	0.92
KE	0.98	0.95
*LAUCI	1.08	0.97
*LAUCT	1.10	0.97
*LCMAX	1.92	0.91
THALF	1.02	1.05
TMAX	0.34	0.93

1=Test-Fast 2=Test-NonFast 3=Ref.-NonFast
UNIT: AUC=μG HR/ML CMAX=μG/ML TMAX=HR THALF=HR KE=1/HR
* The values represent the geometric means (antilog of the means of the logs).

1. Under non-fasting conditions, the mean plasma etodolac levels

reached the maximum around 4 hours (Table #9 and Figures #3 and #4). The absorption rate of the test product under non-fasting conditions was slower compared to the test product under fasting conditions. In general, the results show a significant food effect on the mean plasma levels of etodolac when the drug was given with food.

2. Under non-fasting conditions, the ratios of the test mean to the reference mean (RMEAN2/3) for the log-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were all within the acceptable range of 0.8 to 1.2 (Table #10).

3. The mean LCmax of the test product was reduced by approximately 53%, when dosed under non-fasting conditions compared to fasting conditions (Table#10). This reduction in Cmax value is in agreement with the reference product's labeling which indicated that food intake, reduces the peak concentration reached by approximately one half, and increases the time-to-peak concentration by 1.4 to 3.8 hours.

I. **Adverse Events**:

The adverse reactions are reported on pages #877 and #954, Vol. C1.3, section `Clinical Summary'. The following adverse events summary for study subjects under non-fasting conditions.

Parameter	Test/# subj.	Ref./# subj.
Dizziness	1	--
Headache	--	2
Hot Flashes	1	--
Pharynigits (Sore throat)	1	1
Pain (Sharp pain, right arm)	--	1
Purpura (Hematoma, right arm)	--	1
Rash (left wrist or right forearm)	--	3
Respiratory Disorder (Head Congestion)	1	--
Rhinitis (Runny Nose)	--	2
Syncope (Fainting)	1	--
Tooth Disorder (pain & extraction)	--	1
Vomiting	1	--

Non of the adverse events were considered serious or related in terminating any subject from study participation.

V. **FORMULATION COMPARISON**

Aesgen's comparative formulations for its Etodolac 300 mg capsules are shown in Table #11. The formulation comparison

information are provided on pages #1527 and 1531a, volume C1.5.

Table #11. Formulation

Ingredients	mg/capsule	%w/w
Etodolac	300.00	52.97
Lactose Monohydrate, NF,		
Microcrystalline Cellulose, NF		
Sodium Starch Glycolate, NF		
Povidone , USP		
Sodium Lauryl Sulfate, NF		
Purified Water, USP		
Magnesium Stearate, NF		
Size'O' Gray/Gray Capsule		
TOTAL	566.37	100.00

* Purified water removed during drying process.

VI. DISSOLUTION:

Method: USP 23 apparatus II (Paddles) at 50 rpm
Medium: 900 mL of pH 7.5 phosphate buffer with pancreatin enzyme
Number of Units: 12 Capsules
Test products: Aesgen's Etodolac 300 mg Capsules, lot #MNC0011
Reference products: Wyeth-Ayerst's Lodine® 300mg Capsules, lot #3940275
Specifications: NLT in 45 minutes.

Dissolution testing results are shown in the following Table.

Table 12. In Vitro Dissolution Testing

Drug (Generic Name): Etodolac Capsules
Dose Strength: 300 mg
ANDA No.: 74-929
Firm: Aesgen, Inc.
Submission Date: July 23, 1996
File Name: 74929sd.796

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle:X RPM: 50
No. Units Tested: 12 Capsules
Medium: 900 mL of phosphate buffer (pH 7.5) with pancreatin enzyme
Specifications: NLT in 45 minutes
Reference Drug: Wyeth-Ayerst's Lodine®
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # MNC001V Strength(mg) 300			Reference Product Lot # 3940275 Strength(mg) 300		
	Mean %	Range	%CV	Mean %	Range	%CV
15	70.8		15.4	91.2		5.7
30	94.4		4.1	98.7		1.6
45	97.1		2.9	100.3		0.9
60	97.6		3.3	100.5		1.0

Comment on the Dissolution Data:

1. The dissolution data that are provided on page #1525, volume C1.5 for lot #MNC001V whereas the bioequivalence study was conducted on lot #MNC0011.

2. The dissolution data for the test and reference listed products are not acceptable (see the deficiency section).

VII. COMMENTS:

1. Under fasting conditions: The firm's in vivo bioequivalence study under fasting conditions demonstrated that the test product, Aesgen's Etodolac Capsule 300 mg is bioequivalent to the reference product, Wyeth-Ayerst's Lodine® Capsule 300 mg. The 90% confidence intervals for the log-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were all within the acceptable range of 80-125%.

2. Under non-fasting conditions: The firm's in vivo bioequivalence study under non-fasting conditions demonstrated that the test product, Aesgen's Etodolac Capsule 300 mg is

bioequivalent to the reference product, Wyeth-Ayerst's Lodine® Capsule 300 mg. The ratios of the test mean to the reference mean for the AUC_{0-t}, $AUC_{0-\infty}$, C_{max} were within the acceptable range of 0.8-1.25.

VIII. DEFICIENCIES

1. Dissolution testing conducted by Aesgen Inc. on its etodolac 300 mg Capsules does not meet the agency specifications. The firm has determined dissolution of the test products in 900 mL of pH 7.5 phosphate buffer with pancreatin enzyme, at 37°C using USP 23 apparatus II (Paddles), 50 rpm with limits of not less than (Q), dissolved in 45 minutes, instead of the agency specifications.

   There is no USP dissolution testing procedure specified for etodolac capsules. Therefore, the sponsor should conduct dissolution testing following the Agency specifications.

   The firm should conduct the dissolution testing applying a spectroscopy assay method and using USP 23 apparatus I (Basket) at 100 rpm in 1000 mL of pH 7.5 phosphate buffer at 37°C. The sampling time should be 5, 10, 20 and 30 minutes. The dissolution testing should meet the following specifications:

   > Not less than (Q) of the labeled amount of the drug product in the capsule is dissolved in 20 minutes.

   The dissolution should be conducted for both the test and reference products, performed simultaneously. The lot number of the dissolution testing should be identical to the one used in the in vivo bioeqivalence study.

2. The dissolution data that are provided on page #1525, volume C1.5 are for lot #MNC001V whereas the bioequivalence study was conducted on lot #MNC0011. The firm should check its documents for the correct lot number.

IX. RECOMMENDATION

1. The two in vivo bioequivalence studies (single-dose under fasting and single-dose non-fasting) conducted by Aesgen Inc. on its Etodolac 300 mg Capsule, lot #MNC0011, comparing it to the reference product Wyeth-Ayerst's Lodine® Capsule 300 mg, lot #3940275, have been found to be acceptable to the Division of Bioequivalence. The two studies demonstrate that under fasting and non-fasting conditions, Aesgen's Etodolac 300 mg Capsules are bioequivalent to Wyeth-Ayerst's Lodine® Capsules

300 mg. However, the application is incomplete due the deficiencies cited above.

2. From the bioequivalence standpoint the sponsor has not met requirements of in vitro dissolution testing. The in vitro dissolution testing conducted by Aesgen Inc. on its Etodolac 300 mg Capsules is not acceptable.

3. The firm should conduct the dissolution testing applying a spectroscopy assay method and using USP 23 apparatus I (Basket) at 100 rpm in 1000 mL of pH 7.5 phosphate buffer at 37°C. The sampling time should be 5, 10, 20 and 30 minutes. The dissolution testing should meet the following specifications:

    Not less than (Q) of the labeled amount of the drug product in the capsule is dissolved in 20 minutes.

The firm should be informed of the deficiencies and recommendations.

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE

for RM 3/13/97

Concur: _____ Date: 3/24/97
for Nicholas Fleisher, Ph.D.
Director
Division of Bioequivalence

cc: ANDA#74-929, original, HFD-630 (OGD), HFD-604 (Hare), HFD-658 (Mhatre, Wahba), Drug File
ZZWahba/021197/022897/file#74929s.796

Figure #1

ANDA # 74-929
(Under fasting Conditions)

ETODOLAC 300 MG CAPSULE STUDY (PRACS P95-341; STATS ANALYSES 9631103S)
LEAST-SQUARES MEAN PLASMA ETODOLAC CONCENTRATIONS (N=24)

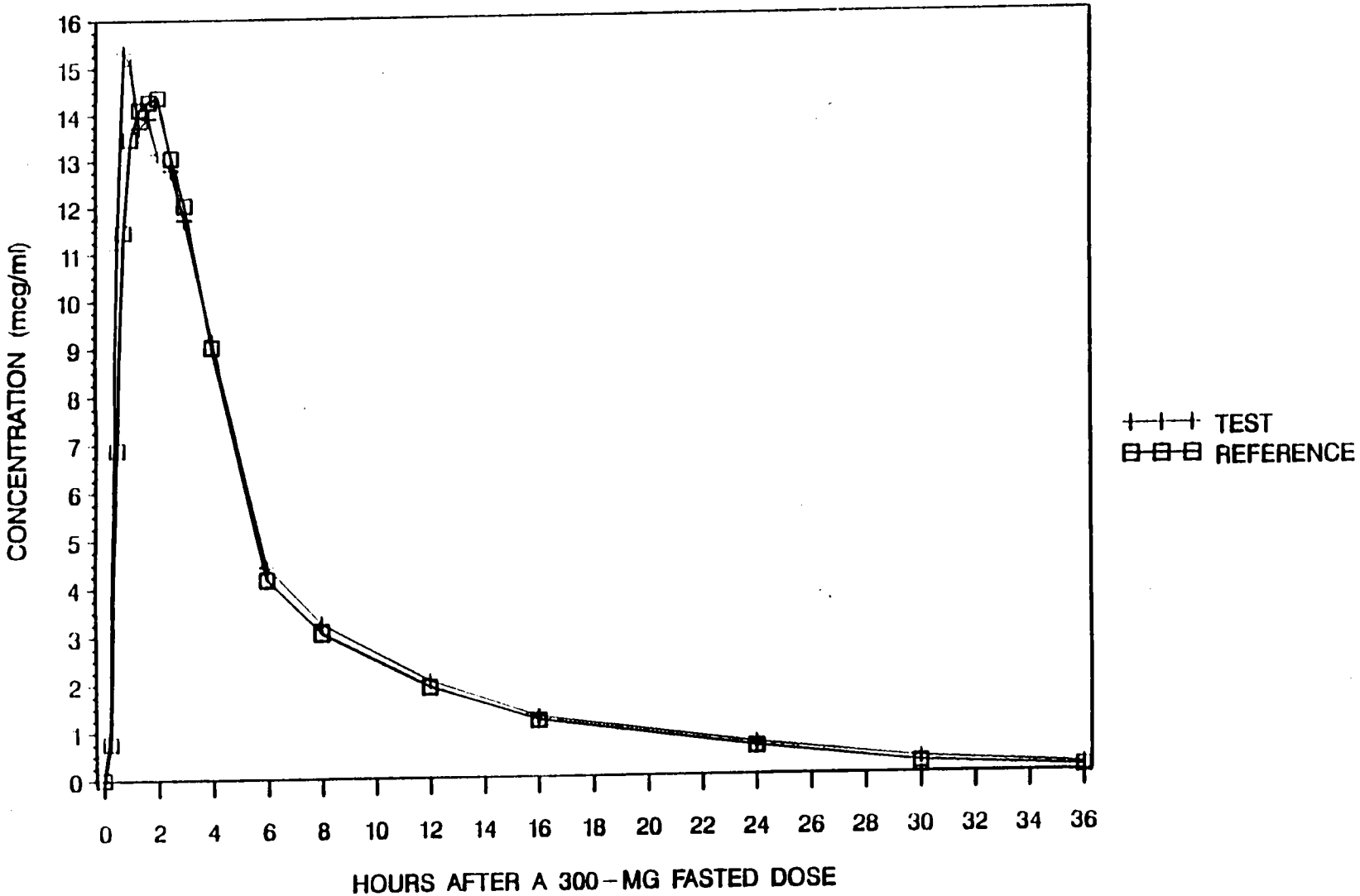


Figure # 2 ANDA # 74-929 (Under fasting Conditions)

ETODOLAC 300 MG CAPSULE STUDY (PRACS P95-341; STATS ANALYSES 9631103S)

NATURAL LOG OF LEAST-SQUARES MEAN PLASMA ETODOLAC CONCENTRATIONS (N=24)

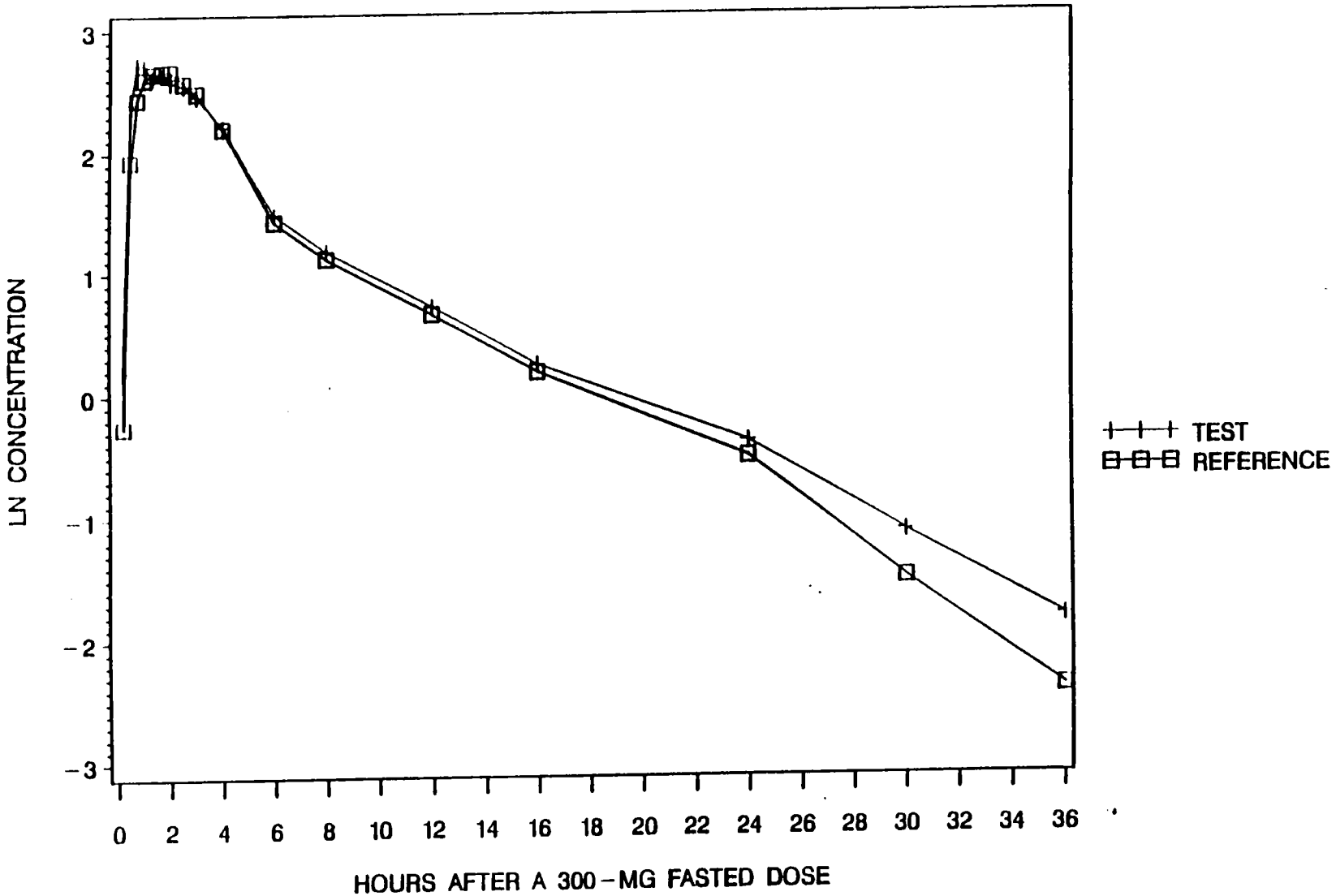


Figure # 3

ANDA # 74-929
(Under Non-fasting Conditions)

ETODOLAC CAPSULE FOOD EFFECTS STUDY (PRACS P95-345; STATS ANALYSES 9631104S)
LEAST-SQUARES MEAN PLASMA ETODOLAC CONCENTRATIONS (N=18)

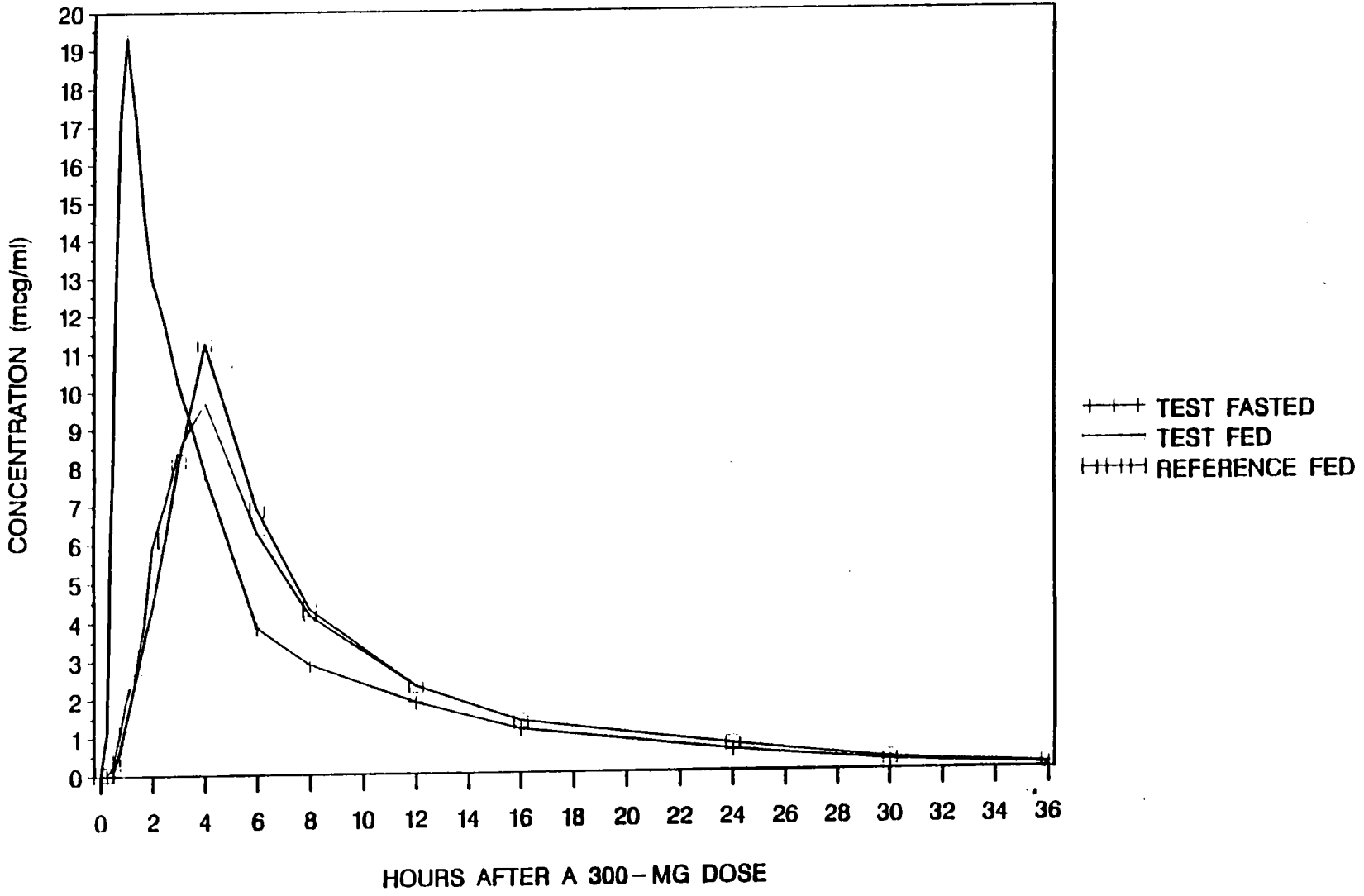
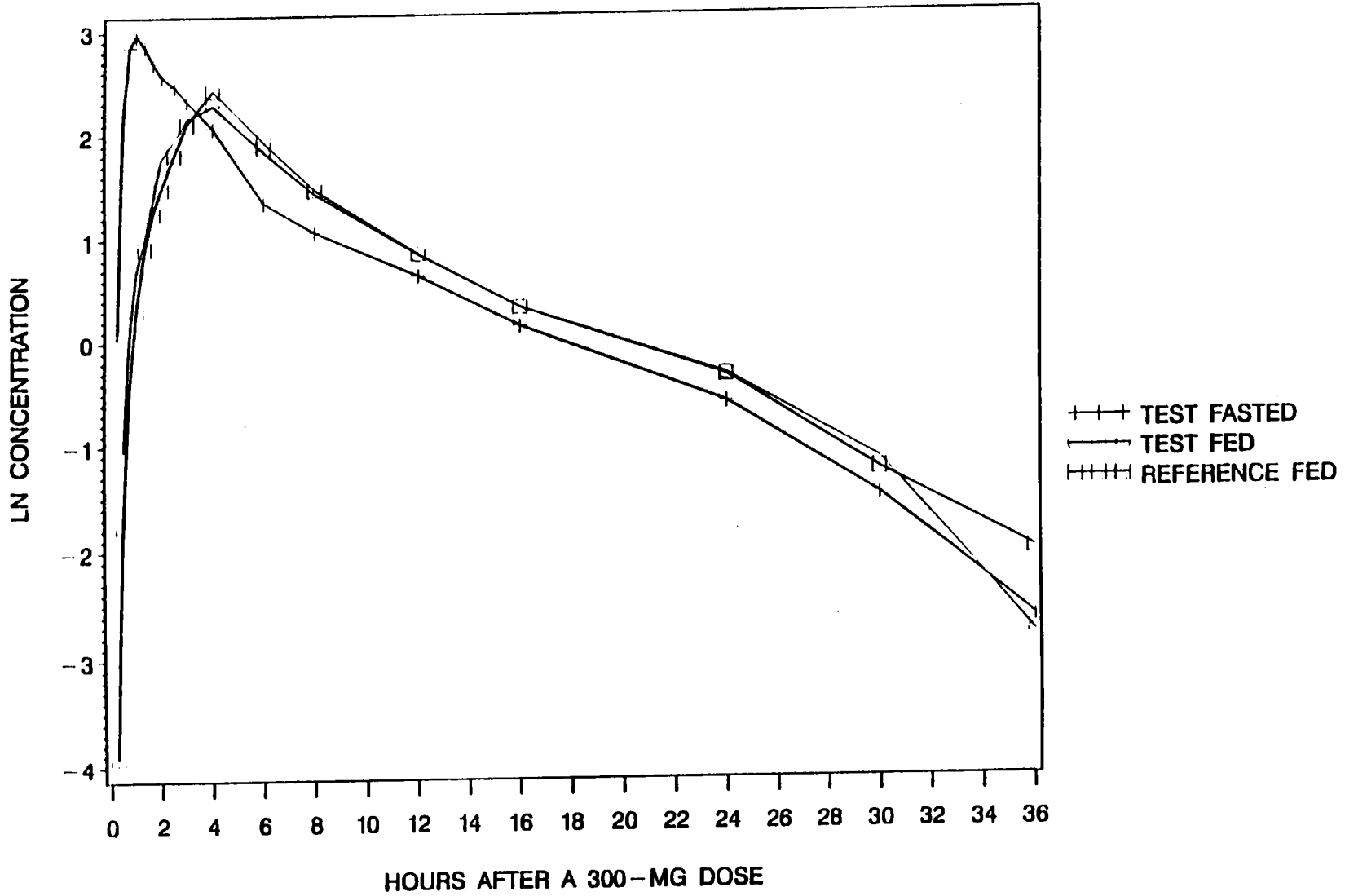


Figure #4

ANDA #74-929
(Under Non-fasting Conditions)

ETODOLAC CAPSULE FOOD EFFECTS STUDY (PRACS P95-345; STATS ANALYSES 9631104S)
NATURAL LOG OF LEAST-SQUARES MEAN PLASMA ETODOLAC CONCENTRATIONS (N=18)



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74929

CORRESPONDENCE

ANDA 74-929

APR - 3 1997

Aesgen, Inc.
Attention: Jeffrey S. Bauer
5051 New Centre Drive
Suite 103
Wilmington NC 28403

Dear Sir:

Reference is made to the Abbreviated New Drug Application, submitted on July 23, 1996 for Etodolac Tablets, 300 mg.

The Office of Generic Drugs has reviewed the bioequivalence data submitted conducted on Etodolac Capsule, 300 mg, lot #MNC0011, comparing it with the reference product Lodine® Capsule, 300 mg, lot #3940275, (Wyeth-Ayerst). The application is incomplete due to the following deficiencies:

1. The dissolution testing conducted on etodolac 300 mg Capsules does not meet the Agency's requirements. There is no USP dissolution testing procedure specified for etodolac capsules. Therefore, the sponsor should conduct the dissolution testing following the Agency's specifications:

   Apply a spectroscopic assay method and using USP 23 apparatus 1 (Basket) at 100 rpm in 1000 mL of pH 7.5 phosphate buffer at 37°C. The sampling times should be 5, 10, 20 and 30 minutes. The dissolution testing should meet the following specifications:

   > Not less than (Q) of the labeled amount of the drug product in the capsule is dissolved in 20 minutes.

   The dissolution should be conducted for both the test and reference products, performed simultaneously. The lot numbers of the samples undergoing dissolution testing should be identical to those used in the *in vivo* study.

2. The dissolution data that are provided on page #1525, volume C1.5 are for lot #MNC001V whereas the bioequivalence study was conducted on lot #MNC0011. The firm should check its documents for the correct lot number.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Lizzie Sanchez, Pharm.D., Project Manager, at (301) 594-2290. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

for Nicholas Fleischer, Ph.D.
Director,
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research